PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:
A61K 33/30, 31/355, 9/06	A1	WO 93/14773
		(43) International Publication Date: 5 August 1993 (05.08.93)

(21) International Application Number: PCT/SE93/00033

(22) International Filing Date: 21 January 1993 (21.01.93)

(30) Priority data:
9200199-9 24 January 1992 (24.01.92) SE

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(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).

Published
With international search report.
With amended claims.
In English translation (filed in Swedish).

(54) Title: PHARMACEUTIC COMPOSITION AND ITS USE

(57) Abstract

The present invention relates to a pharmaceutical composition, e.g. an ointment, a cream or a paste, which can be used to treat superficial skin and mucous membrane affections. The composition is a mixture, which comprises, in percent by weight: 5-60% ZnO; 10-70% of one or several of the substances, which belong to one or several of the groups disaccharides, monosaccharides and glycosides; and 3-30% vitamin E; the rest being mainly only pharmaceutically acceptable vehicles.

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Pharmaceutic Composition and Its Use.

The present invention relat s to a pharmaceutical composition, e.g. an ointment, a cream or a paste, which can be used to treat superficial skin and mucous membrane affections. The invention also relates to the use of this composition to produce a pharmaceutical preparation designed to treat such superficial affections. This preparation may be used to treat human beings as well as animals.

BACKGROUND ART

It has been known for a long time, that zinc oxide has a positive effect on the healing of sores. In vitro-examinations have shown, that zinc oxide has a beneficial antimicrobial effect, is astringent and locally protective as well as antiphlogistic and antipruritic. Zinc oxide is used today in various ointments, pastes and creams in order to treat skin lesions. SE 451 669 relates to the use of zinc oxide in dressings in order to clean sores and stimulate their healing, the zinc oxide in the dressing being bound by means of a tissue-compatible polymer.

It has also been reported, that certain types of sugar, i.a. saccharose, $C_{12}H_{22}O_{11}$, has a positive effect on sore healing. Much research is needed regarding the underlying causes, but it is true that sugar is able to bind bacteria and virus. An environment with a low water activity in the sore is obtained, which can stop or reduce the bacterial growth. Adding sugar to an infected sore probably gives the bateria an osmotic shock. Also, it has been found, that sufficient amounts of sugar block the lecithins of the microorganisms and consequently prevent the microorganisms from being bound by the receptors of the cellular surface. Thus, a sugar ointment is used successfully against acute mediastinitis subsequent to heart surgery operations, against severe burns etc. In addition to disaccharides such as saccharose, meltose and cellobiose, all of which have the molecular formula $C_{12}H_{22}O_{11}$, probably also monosaccharides such as hexoses, e.g. glucose, fructose or galactose, all

of which have the structural formula $C_6H_{12}O_6$ and certain glycosides are active.

It is also known that vitamin E is an excellent antioxidant and is able to contribute to the stability of the cell membranes by protecting the polyunsaturated fatty acids in the lipids of the membrane against attacks by free radicals.

BRIEF DISCLOSURE OF THE INVENTION

Thus, the active effect of zinc oxide on certain skin and mucous membrane affections has been thoroughly documented and terapeutic effects of certain types of sugar on sore treatment have been reported. Also, the effect of vitamin E as an antioxidant is known per se. However, these substances apparently have not been utilized in an optimal way for the treatment of superficial skin and mucous membrane affections. For the treatment of e.g. skin-fold dermatitis (angular cheititis, cheititis, intertrigo), bed sore and acne vulgaris there is a need of agents, which are cosmetically acceptable and at the same time more active than those which are available today. Also, for the treatment of other superficial sores such as bed sores and burns there is a need of improved preparations. In the veterinary field there is a need of improved preparations designed for the treament of various skin lesions, e.g. sores which are slow in healing, skin-fold dermatitis and blisters (dogs, horses) as well as greasy heels on horses.

The purpose of the invention is to meet these needs, which can be done by means of a pharmaceutical composition, which consists of a mixture, which comprises zinc oxide (ZnO), one or several of the substances, which belong to any of the groups disaccharides, monosaccharides and glycosides as well as vitamin E in effective amounts in a pharmaceutically and cosmetically acceptable vehicle, which gives the mixture the consistency of an ointment, cream or paste, Also, the mixture can and ought to include at least one or seve-

ral of the substances zinc sulphate ($ZnSO_4$), vitamin A and boric acid (H_3BO_3).

Zinc oxide has in in vitro-examinations proved to have a satisfactory antimicrobial and antidermatophytic effect. It is also astringent and locally protective, antiphlogistic and antipruritic and ought to be included in the composition in a minimum amount of 5 percent by weight, preferably at least 15 percent by weight and suitably at least 20 percent by weight in order to obtain the desired effect. The maximum amount depends on the consistency requirements and is not more than 60 %, preferably not more than 50 %, suitably not more than 45 %. An optimal amount is about 30 or not more than 35 percent by weight.

The composition according to the invention is to include some type of sugar. Saccharose which is a disaccharide with the molecular formula $C_{12}H_{22}O_{11}$, and particularly glucose, which is a monosaccharide (hexose) with the structural formula $C_6H_{12}O_6$ have proven to be active. Also, certain glycosides can be considered as alternatives or supplements to disaccharides and/or monosaccharides. Consequently, in accordance with a further way of defining the composition of the present invention one or several of the substances, which belong to any of the groups disaccharides, monosaccharides and glycosides, are to be included in it in an amount of 10-70 percent by weight, preferably 10-50 percent by weight and suitably 15-45 %. An optimal amount is 15-35 %.

Vitamin E is an excellent antioxidant and contributes to the stability of the cell membranes by protecting the polyunsaturated fatty acids in the lipids of the membrane from attacks by free radicals and oxidation. Vitamin E appears in the composition according to the invention, due to its protective action, to provide a synergistic effect in combination with zinc oxide and the above-mentioned type(s) of sugar. Consequently, vitamin E ought to be included in a

minimum amount of 5 percent by weight and suitably at least 10 percent by weight in order to obtain said effects to the desired extent. The maximum amount may be as high as 30 % and suitably not more than 20 %. An optimal amount is about 15 percent by weight.

A preferred vehicle (carrier) is the so called Essex cream, which is a trade name for a fatty cream, which in addition to the main components vaseline and liquid paraffin includes emulsifiers as well as preservatives and pH value-adjustment agents. Other suitable vehicles are e.g. pure vaseline, Locobase and cod liver oil (the latter mainly for veterinary use).

The above-mentioned ingredients are unconditional substances in the composition according to the invention. The conditional substances, which preferably are to be included in the composition, can be added in the following concentrations:

Zinc sulphate, which is astringent and antiphlogistic, can and ought to - dissolved in a small amount of water - also be used in a minimum amount of 0.5 %, not more than 3 %. An optimal amount is about 1 percent by weight.

Vitamin A is important for the growth and the function of epithelial tissues of the skin and ought to be included in the composition in a minimum amount of 0.01 and mot more than 3 percent by weight, preferably not more than 1 percent by weight, suitably not more than 0.5 percent by weight. A suitable amount is about 0.2 percent by weight.

Boric acid, which denatures proteins, is astringent and antiseptic, bacteriostatic and fungistatic, can be added in a minimum amount of 0.5 %. However, it is true that boron compounds may have certain adverse effects, e.g. having an irritating effect on mucous membranes, and consequently, boric acid should not be added in a larger amount than 3

percent by weight. An optimal amount is about 1 percent by weight.

In in vitro-examinations and clinical examinations, which were performed on human beings, dogs and horses and which will be reported below, an ointment was used, which for each 100 g comprises 32 g ZnO, 1 g $ZnSO_4$ in water solution, 25 g glucose, 1 g H_3BO_3, 15 g vitamin E (tokoferoliacetas (alfa) 20.400 IE), 0.2 g vitamin A (retinolipalmitas 0.34 mil IE) and the rest a pharmaceutically and cosmetically acceptable vehicle, more particularly an Essex ointment, which includes about 0.5 % chlorocresol as a preservative.

In vitro-examinations

The antimicrobial activity of a cream having the above-mentioned composition against Pityrosporum ovale ATCC 42132,44031, Candida albicans H 29, Staphylococcus aureus, Streptococcus haemolytica as well as Propionebacterium acnes were evaluated. DST-agar with added Tween 80 (2 ml/l) as well as glycerine monostearate (2.5 g/l) was used as a test medium for P. ovale. DST-agar without these additives was used for C. albicans, S. aureus, St. haemolytica and Pr. acnes.

The cream according to the invention was added to the DST-medium, with and without additives, concentrations of 40, 20, 10, 5, 2.5, 1 and 0.5 % of the cream in the agar-medium being obtained. Control plates were made with distilled water. Plates were inoculated with 10^8 cells/ml (0.1 ml) of P. ovale. The rest of the microorganisms were inoculated in a concentration of 10^6 cells/ml (0.1 ml). P. ovale was read after an incubation of 3 days. Pr. acnes was incubated anaerobicly and was read after 2 days. The rest of the bacteria and C. albicans were read after an incubation time of 1 day. The plates incubated at 37°C. The least inhibitory concentration (MIC) was registered for the minimum concentration of the cream according to the invention, at which a total growth inhibition could be registered.

Table 1 shows the MIC-values for various microorganisms. St. haemolytica was the most susceptible organism with a MIC-value of 0.5 %, whereas C. albicans was the most resistant with a MIC-value of 10 %. The study shows that the cream according to the invention is active in vitro against a plurality of microorganisms , which are found in many skin affections, e.g. those mentioned above and impetigo, acne vulgaris as well as Pityrosporum-related problems, including seborrhoeic dermatitis, pityriasis versicolor and cutaneous candidiasis.

Table 1

Activity in vitro of a cream according to the invention against various microorganisms (MIC = minimum inhibitory concentration of the preparation according to the invention)

Microorganisms	MIC (%)
P. ovale ATCC 42132	2.5
P. ovale ATCC 44031	2.5
C. albicans H 29	10
S. aureus	2.5
St. haemolytica	0.5
Pr. acnes	5

Treatment of acne vulgaris

The cream according to the invention as a local treatment-agent for a mild form av acne vulgaris was evaluated. The study was performed at the skin department of a large Swedish hospital. Patients having a mild form of acne were selected. After a washout-period of two weeks the treatment with the cream was started, the cream having the same composition as in the in vitro-examination, in the morning and in the evening in an open procedure. The patients were evaluated on day 0, day 7, days 14-21 as well as days 35-42 at the skin department. The number of papules and pustules in the face was counted at every visit. 48 patients in all were treated in this way, 20 men and 28 women, the patients be-

ing 15-35 years old. The results are set forth in Table 2 below. The table shows, that this cream according to the invention has a satisfactory effect on the number of papules and pustules, when a mild acne in treated.

Table 2

Mean values of the number of lesions in the face of treated patients having a mild acne :

	day 0	day 7	day 35-42
papules	24	20	10
pustules	14	8	4

Test on dogs

60 dogs in all of different breeds participated in the study, which was performed in an animal hospital. The diagnoses were classified into the following 5 groups:

Group 1 skin-fold dermatitis;
2 blisters after plaster or dressings;
3 scurs hosp/cracked pads ;
4 sores slow in healing; and
5 other skin lesions.

The cream had the same composition as the cream used to test acne and was applied by the animal owner 1 or 2 times a day after a cleaning of the sore. A control of the results was carried out after a week and in some cases after two weeks in the animal hospital. Due to a substantial travel distance to the hospital the results in a few cases were reported by the animal owner on the telephone. The evaluation of the results was made on a scale of 1-4 and by one and the same person according the following:

4	Very excellent	The result visible after one day. The lesion is healed within one week.
3	Excellent	The result is visible after 2-3 days. The lesion is healed within 2 weeks.

2	Satisfactory	The result is obvious, but it takes more than 2 weeks for the lesion to heal.
1	Not satisfactory	No or small improvement after a treatment for 10 days.

The results have been compiled in Table 3.

Table 3

A compilation of the results of tests on dogs:

Diagnosis	Number	Evaluation			
		4	3	2	1
skin-fold dermatitis	11	9	1	1	
blisters	6	6			
scurs hosp/cracked pads	3				3
sores slow in healing	24	9	10	5	0
other skin lesions	16	9	2	1	4

The results show that the cream according to the invention has an excellent healing effect on skin sores on dogs. The preparation also has an excellent adherence to the skin and the sore. When the cream has been used on infected sores below plaster casts, the cream has after a cleaning of the sore been applied and new plaster cast has then been applied. During the next plaster cast the sores have been healed. Excellent results have also been obtained for large skin sores. They will heal quickly after the cream has been applied. Various types of skin-fold dermatitis heal without exception very fast. The cream was also tested on 7 dogs, operated on for anal fistula. The cream was applied on the open sore. Since the sores were large, it took in some cases more than 14 days to heal. However, in all those 7 cases a considerably better and quicker healing could be observed with the cream than without. The cream showed less excellent results on scurs hosp, cracked pads and excema on paws.

Tests on horses

The same sore cream was used as in the previous examinations. 94 horses having various skin lesions participated in the study. Among these 55 have had pastern dermatitis, whereas others have had sores of various types.

The cream was applied by a veterinary or a horse owner. The applications were done after a cleaning of the sore 1-2 times every day. During the 2-5 first applications in most cases a light-weight dressing has been applied on top of the cream. During the subsequent applications no sore dressing has been used, only the cream. The number of applications for every treatment, i.e. up to a healing or up to the moment when the treatment has been discontinued (namely in those 8 instances when no healing could be observed), has varied between 4-13 applications.

Tested skin lesions as well as the bases for forming the evaluations of the healing result are shown in Table 4. The compilation is based on the data, which have been reported by the veterinaries.

Table 4

Diagnosed skin lesions on 94 horses, which were treated with the cream according to the invention. Evaluation scale: +++ = the lesion is healed within one week; ++ = the lesion is healed within two weeks; + = the result is obvious, but it takes more than two weeks to heal; - = no or a minor improvement after a treatment for two weeks:

	Treated cases	Healing effect	
sores, pastern dermatitis, greasy heal, liguid	55	+++	in 42 cases
		++	10
		-	3
sores, pastern deramtitis, greasy heal, dry	13	+++	6
		++	5
		-	2

blisters	6	++	6
sores, "large"	5	++	5
sores,superficial	8	+++	5
		-	3
shuffle sores	6	+++	6

It is shown in Table 4, that the cream has a desired effect, particularly on greasy heel. No side effects have been reported.

CLAIMS:

1. A pharmaceutical composition such as an ointment, a cream or a paste, which can be used to treat superficial skin and mucous membrane affections, characterized in that it is a mixture, which comprises, in percent by weight,
5-60 % ZnO;
10-70 % of one or several of the substances which belong to any or several of the groups disaccharides, monosaccharides and glycosides;
3-30 % vitamin E, and
the rest being mainly only a pharmaceutically acceptable vehicle.

2. A composition according to claim 1, characterized in that it comprises at least 15, preferably at least 20 and not more than 50 %, preferably not more than 45 % ZnO.

3. A composition according to claim 1, characterized in that it comprises 10-50 %, preferably 15-45 %, suitably 15-35 % of one or several of the substances, which belong to any or several of the groups disaccharides, monosaccharides and glycosides.

4. A composition according to claim 3, characterized in that it comprises at least 10 % of one or several disaccharides.

5. A composition according to any of claims 1 and 4, characterized in that said monosaccharides mainly are one or several hexoses in an amount of at least 10 %, preferably glucose.

6. A composition according to claim 5, characterized in that it comprises at least 5, preferably at least 10 and not more than 20 % vitamin E.

7. A composition according to any of claims 1-6, c h a r a c t e r i z e d in that it comprises 0.5-3 % $ZnSO_4$, preferably not more than 2 % $ZnSO_4$.

8. A composition according to any of claims 1-7, c h a r a c t e r i z e d in that it comprises 0.01-3 % vitamin A, preferably not more than 1, suitably not more than 0.5 % vitamin A.

9. A composition according to any of claims 1-8, c h a r a c t e r i z e d in that it comprises 0.5-3 % H_3BO_3, suitably not more than 2 % H_3BO_3.

10. A composition according to any of claims 1-9, c h a r a c t e r i z e d in that 100 g of the composition nominally comprises about 30 g ZnO, about 1 g $ZnSO_4$ in water solution, about 25 g glucose, about 1 g H_3BO_3, about 15 g vitamin E (tokoferoliacetas (alfa)) , about 0.2 g vitamin A (retinolipalmitas), the rest being pharmacologically and cosmetically acceptable vehicles.

11. A use of the composition according to any of claims 1-10 in order to produce preparations for treatment of superficial skin and mucous membrane affections.

12. A use according to claim 11 in order to produce preparations for sore treatments, particularly for treatment of skin-fold dermatitis (angular cheilitis, cheilitis, intertrigo and decubitus).

13. A use according to claim 11 in order to produce preparations for treatment of acne.

14. A use according to claim 11 in order to produce preparations for pretreatment of superficial skin and mucous membrane affections in animals.

AMENDED CLAIMS

[received by the International Bureau on 28 June 1993 ((28.06.93); original claim 3 amended; other claims unchanged (1 page)]

1. A pharmaceutical composition such as an ointment, a cream or a paste, which can be used to treat superficial skin and mucous membrane affections, c h a r a c t e r i z e d in that it is a mixture, which comprises, in percent by weight,
5-60 % ZnO;
15-45 % of one or several of the substances which belong to any or several of the groups disaccharides, monosaccharides and glycosides;
3-30 % vitamin E, and
the rest being mainly only a pharmaceutically acceptable vehicle.

2. A composition according to claim 1, c h a r a c t e r i z e d in that it comprises at least 15, preferably at least 20 and not more than 50 %, preferably not more than 45 % ZnO.

3. A composition according to claim 1, c h a r a c t e r i z e d in that it comprises 15-35 % of one or several of the substances, which belong to any or several of the groups disaccharides, monoaccharides and glycosides.

4. A composition according to claim 3, c h a r a c t e r i z e d in that it comprises at least 10 % of one or several disaccharides.

5. A composition according to any of claims 1 and 4, c h a r a c t e r i z e d in that said monosaccharides mainly are one or several hexoses in an amount of at least 10 %, preferably glucose.

6. A composition according to claim 5, c h a r a c t e r i z e d in that it comprises at least 5, preferably at least 10 and not more than 20 % vitamin E.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00033

A. CLASSIFICATION OF SUBJECT MATTER

IPC5: A61K 33/30, A61K 31/355, A61K 9/06
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC5: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO, A1, 8402845 (ADVANCED DRUG TECHNOLOGY CORPORATION), 2 August 1984 (02.08.84), the claims --	1-14
Y	ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Volume 23, No 5, May 1983, Jorge Chirife et al, "In Vitro Study of Bacterial Growth Inhibition in Concentrated Sugar Solutions: Microbiological Basis for the Use of Sugar in Treating Infected Wounds" page 766 - page 773 --	1-14
Y	JOURNAL OF THE MEDICAL ASSOCIATION OF THAILAND, Volume 69, No 7, 1986, Kasian Bhanganada et al, "The Use of Super - Saturated Sucrose Solution for Chronic Skin Ulcers" page 358 - page 366 --	1-14

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
26 April 1993	03 -05- 1993
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 93/00033

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Jorge Chirife et al, "Scientific basis for use of granulated sugar in treatment of infected wounds", 1982, THE LANCET, page 560 - page 561	1-14
A	Chemical Abstracts, Volume 113, No 10, 3 Sept 1990 (03.09.90), (Columbus, Ohio, USA), United States Food and Drug Adm., "Skin protectant drug products for over-the-counter human use; proposed rulemaking for diaper rash drug products", page 404, THE ABSTRACT No 84672h, Fed.Regist. 1990, 55 (119), 25204-25232	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

31/03/93

International application No.
PCT/SE 93/00033

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A1- 8402845	02/08/84	CA-A- 1243951	01/11/88
		EP-A- 0133437	27/02/85